Chapter 8

General Discussion
This thesis is a result of the Netherlands XTC Toxicity (NeXT) study, which investigates the causality, course and clinical relevance of the neurotoxicity of ecstasy or +/-3,4-methylenedioxymethamphetamine (MDMA). In 2006 and 2007 two other NeXT-dissertations were published about the main neuro-imaging findings in ecstasy users; one on fMRI results and one on MRI/SPECT results \(^{51,108}\). According to these theses, heavy ecstasy use was associated with altered memory-related brain activity and a specific neurotoxic effect on the thalamus was found. In addition, it was found that low dose ecstasy use was associated with sustained changes in brain perfusion, without strong evidence for axonal damage or altered brain activity \(^{51,108}\). One of the remaining questions of the NeXT study was whether these neuro-imaging findings were paralleled by clinically observable deficits. The main objective of the current thesis was to elucidate the specific sustained effects of ecstasy on neuropsychological functioning. It allows for the potential confounding effects of other drugs and pre-existing differences that might have impinged on previous ecstasy-studies with cross-sectional designs and a lack of control for the role of polydrug use.

The main finding of the current thesis was a sustained negative effect of ecstasy on verbal memory (chapter 3, 4, and 6). This result was obtained by both cross-sectional study designs in polysubstance users (chapter 3 and 6), and by a prospective study design in novice ecstasy users with minimal exposure to other drugs (chapter 4). Even first use of a small dose of ecstasy was associated with decreased verbal memory function (chapter 4). This negative effect of ecstasy on verbal memory adds to age-related memory decline, as shown by a study in middle-aged (ex-)ecstasy users (chapter 6). Moreover, an indication for individual differences in genetic vulnerability was found; the extent of verbal memory decrement was moderated by a functional polymorphism in the catechol-O-methyltransferase (COMT) gene (chapter 5). Differences in punishment sensitivity or reflection of negative feedback might predispose to the first use of ecstasy; this conclusion was based on a study with a prospective design (chapter 7).

**Effects of ecstasy on verbal memory**

We found a negative effect of ecstasy use on verbal memory, which is well in line with numerous previous studies (for review and meta-analyses: \(^{84,117,123,255}\)). This finding might point to a specific effect of ecstasy on brain areas that are involved in learning and memory. For example, one recent study from the NeXT project showed strong evidence of a neurotoxic effect of heavy ecstasy use on the thalamus \(^{46}\), a brain area that is important for memory function \(^{252}\). Also other studies \(^{33,35,65,66,88,100,107,198}\) gave support for an effect of ecstasy on brain areas that are involved in learning and memory, like prefrontal and medial temporal areas, and in particular the hippocampal area \(^{21,213}\). The COMT gene seemed to play a role in the extent of verbal memory decrement after ecstasy use (chapter 5). COMT is especially present in the prefront cortex and possibly also in the hippocampus \(^{135,242}\), areas associated with learning and memory. Apart from verbal memory deficits, no other neuropsychological deficits were found. However, there is a possibility that we missed effects on these other neuropsychological functions; the tests we used may not have been sensitive enough. It could, therefore, be valuable to add other tests that might capture such deficits better. It is also conceivable that inconsistent
findings concerning other cognitive domains than verbal memory, might be due to exposure to or an interaction with drugs other than ecstasy.

**Effect of ecstasy or other substances**

The different study designs that were used in this thesis allowed us to distil the specific effect of ecstasy from the effects of other substances. This is important because a major problem in investigating the effects of ecstasy is that almost all ecstasy users use other substances as well. Therefore, effects that have been ascribed to the use of ecstasy could in fact have been caused by other drugs, or by a combination of ecstasy and other drugs. Several ecstasy studies tried to minimize the confounding effects of other drugs either by excluding users with concomitant drug use other than ecstasy, by including a polydrug group with drug use patterns comparable to the ecstasy group, or by statistically adjusting for the effects of other drugs. However, these attempts have limitations because ‘pure’ ecstasy users barely exist and the amount of drug use in the control groups appeared to be generally lower than in the ecstasy groups. Statistically controlling for the use of other drugs than ecstasy was usually hampered by strong correlations between ecstasy use and other drug use, leading to multi-collinearity and impossibility to adjust for these potential confounders in statistical analyses. We tried to overcome these limitations by: studying a population with such a variation in type and amount of drug use that correlations between the use of ecstasy and other substances were relatively low allowing a valid interpretation of the results of multiple linear regression models; studying ecstasy users and controls with only minimal exposure to other drugs; and comparing ecstasy-polydrug users with an ecstasy-naive group that used comparable amounts of substances other than ecstasy. The multiple linear regression models in the cross-sectional study provided interesting information about the separate effects of different substances on cognitive functioning, besides the specific effects of ecstasy. While ecstasy particularly affected verbal memory, it appeared that visual memory and visuospatial ability were mainly affected by amphetamine. Also alcohol negatively affected verbal memory, but to a lesser extent than ecstasy. Surprisingly, cannabis had a positive effect on verbal memory; this effect could be ascribed to cannabis users also using ecstasy and not to ecstasy-naive cannabis users. Knowing that in many previous ecstasy-studies, ecstasy use was highly correlated with the use of other substances, the study described in illustrates that these substances can be important confounders, as they affect cognition too. In addition, the cross-sectional comparison between middle-aged ecstasy-polydrug users and middle-aged ecstasy-naive polydrug users showed that besides the specific effect of ecstasy on verbal memory, both groups reported more psychopathological symptoms than a drug-naive control group. This indicates that drugs other than ecstasy influence mood, and thus can be major confounders in most studies on the effects of ecstasy on psychological functioning.

Still, a limitation in these cross-sectional studies is the possibility of pre-existing differences affecting the study results. It remains uncertain whether differences in neuropsychological functioning are the result of ecstasy use or already existed before the first use of ecstasy.
Pre-existent differences or consequence of ecstasy use

Owing to the innovative prospective design of the NeXT study, it was possible to eliminate the confounding problem of potential pre-existent differences. Our study in novice ecstasy users (chapter 4) showed that decreased verbal memory performance did not precede first ecstasy use, but developed after the first use of ecstasy. However, this was not a randomized trial and an undefined confounding factor not (adequately) measured may still have influenced the findings. For example, in chapter 7 we highlight potential predictive factors that might predispose to the first use of ecstasy. Decision-making strategies were predictive for future ecstasy use in female participants. Also, it appeared that insensitivity to negative feedback predicted future ecstasy use, in both male and female ecstasy users. Therefore, an important question is whether decision-making parameters before first ecstasy use are related to verbal memory performance after first ecstasy use. Post hoc analyses showed that there was no relationship between decision-making parameters before first ecstasy use and verbal immediate and delayed recall after first ecstasy use. However, it appeared that in the group of future ecstasy users, insensitivity to negative feedback before first ecstasy use was significantly associated with a decrease in verbal memory recognition after first ecstasy use (r=0.2; p=0.04). This association was, however, restricted to male future ecstasy users (males r=0.5; p=0.01; females r=0.2; p=0.20). Thus, some differences in feedback processing might predispose future male ecstasy users to make more mistakes in verbal memory recognition once they have started to use ecstasy. However, this conclusion is somewhat tentative, because the association was rather weak and only concerned males’ performance on one memory subtask. It, therefore, offers no satisfying explanation for the overall findings of decreased verbal memory in both male and female ecstasy users. Important to keep in mind is that, in our prospective study, verbal memory performance did not differ between future ecstasy users and persistent ecstasy-naives before the first use of ecstasy. Hence we conclude that pre-existing differences in memory are no sufficient explanation for the verbal memory deficits found in ecstasy users.

Dose-response relationship

We did not consistently find a dose-response relationship. In chapter 3, a dose-response relationship was found between the amount of lifetime ecstasy use and verbal memory in heavy ecstasy users with a mean lifetime ecstasy use of 327 tablets (mean age 23.5; r=-0.4; p=0.02). In novice low dose ecstasy users a mild dose-response relationship was found between the amount of lifetime ecstasy use (mean 3.2 tablets) and verbal memory (mean age 22.7; r=-0.3; p=0.02) (chapter 4). In contrast, in a middle-aged sample (mean age 45.6) there was no relationship between lifetime amount of ecstasy use (mean 888 tablets) and verbal memory (chapter 6). Perhaps, the study sample in chapter 6 was too small to detect a dose-response relationship (n=17). However, similar inconsistencies can be found in the rest of the ecstasy-literature. These inconsistencies might be due to small sample sizes or lack of variation in the amount of ecstasy use. It is also possible that it does not matter how much ecstasy is used above a certain threshold, or that it only matters if ecstasy is used. For example, in squirrel monkeys a single MDMA dose resulted in long term serotonin depletion. Human studies on the sustained neuropsychological
effects of low dose ecstasy use are scarce. Our own prospective study showed negative effects of low dose ecstasy (mean 3.2 tablets) on verbal memory (chapter 4). An alternative explanation for the inconsistencies in finding a dose-response relationship is given in chapter 5, which points to individual differences in genetic vulnerability to the harmful effects of ecstasy.

Clinical relevance

Although this thesis provides converging evidence for a negative effect of ecstasy on verbal memory, the clinical relevance of this finding is not immediately clear. Overall test performances remained within the normal range of a sex- and age-comparable general population. Therefore, it seems not (yet) justified to sound the alarm. However, looking at the individual level, it appeared that some subjects in the ecstasy using groups did not perform within the normal range, but at least one and half a standard deviation below the norm, whereas in the ecstasy-naive groups there were hardly any subjects performing that poor [three subjects out of 31 young frequent ecstasy users versus zero subjects of the 36 ecstasy-naives (chapter 3); three subjects out of 58 novice low dose ecstasy users versus zero subjects of the 60 ecstasy-naives (chapter 4); eight subjects out of 17 middle-aged ecstasy users versus one of 16 polydrug users, and one of 20 drug-naives (chapter 6)]. The overall group effect size of the influence of ecstasy use on verbal memory was found to be in the order of half a standard deviation, which also is not negligible. Probably, an ecstasy user may not notify decreased memory functioning in daily life. However, hypothetically, a brilliant young man or woman with high learning capacities might give in a little, leading to suboptimal functioning in high-demanding jobs and reduced career prospects. Although we did not find an age by ecstasy interaction effect on verbal memory in a middle-aged sample (39 to 55 yrs), the study provided some evidence for the irreversibility of verbal memory decrements related to ecstasy use (chapter 6). If the effects turn out to be permanent, long term consequences like clinically relevant early age-related memory decline later in life, cannot be excluded.

Some authors advocate the study of controlled use of low dosages of MDMA as a therapeutic adjuvant to psychotherapy in the treatment of post-traumatic stress disorder or untreatable anxiety in terminal cancer patients. These clinical trials might reveal significant and relevant positive effects of MDMA in otherwise untreatable patients, which outweigh the potential negative effects of MDMA. For such applications of MDMA one should make a well-considered risk-benefit analysis, taking the negative effects on memory and other potential harmful side-effects into account.

Strengths and limitations

The major strength of this thesis concerns the study designs, of which the prospective design is the most innovative. The prospective nature of the study described in chapter 4 demonstrates that decreased verbal memory performance in ecstasy users is not pre-existent. This design also offered the opportunity to investigate potential predictors for first ecstasy use. Furthermore, the relatively low correlations between the different
Chapter 8

substances that were used by the participants in chapter 3 made it possible to look at the contributions of different substances that often confound the observed effects of ecstasy on cognitive functioning. Finally, the study in middle-aged ecstasy users adds to the knowledge base in the field, because this group had not been studied before. However, there are also limitations that need to be considered when interpreting the findings described in this thesis.

One of the limitations is that we had to rely on self-report drug use histories. Hair analyses were used in a part of our participants, but hair analyses do not provide information about frequency or dosage. Furthermore, there was no control on the purity of the ecstasy tablets that were used by the subjects. However, results from pill-testing services in the Netherlands showed that in 2002-2004 in 95% of the tablets sold as ecstasy, MDMA was the main component. This percentage might have been somewhat lower in the ecstasy tablets used by the middle-aged participants in chapter 6, because in the 1980s there was no control on the content of ecstasy tablets yet.

Due to the naturalistic design of the study, potential confounding of lifestyle differences cannot be totally excluded. For example, we did not take into account the environmental circumstances in which the drug was used, like ambient heat and dehydration, was not investigated, nor did we investigate the effect of different drugs used at the same time. Influence of these factors may play a role in the neuropsychological damage due to ecstasy. However it would be almost impossible to control for all these factors.

Another limitation is the selection of subjects. None of the samples, except for the middle-aged sample in chapter 6, was probably fully representative for the population of ecstasy users, which might limit the generalizability of the results. The subjects participated in a fairly demanding research project, including interviews, brain imaging and blood sampling (results reported in several papers). This most probably induced selection of highly motivated subjects. Moreover, subjects with higher education were more likely to participate in the NeXT study than subjects with lower levels of education. However, according to the brain reserve hypothesis, it is more difficult to determine decreases in cognitive functioning in higher educated people than in lower educated persons. This implies that our findings may represent an underestimation of the effect of ecstasy.

Furthermore, we did not use a correction for multiple comparisons in all studies. We included several neuropsychological tests that have shown to be sensitive to ecstasy-related neurotoxicity and that are related to functions or brain areas that are thought to be affected by ecstasy use (e.g. prefrontal cortex, occipital cortex, hippocampus). Analyzing multiple dependent variables increases the probability of Type I errors (incorrectly finding of a positive result). However, using Bonferroni corrections for every performed test would have been too conservative, first because Bonferroni corrections assume independence between the dependent variables, which is not the case in our studies, and second because all tests and analyses were chosen based on a priori explicit hypotheses. Moreover, in the prospective studies we expected a priori small effects because we studied early indicators of potential ecstasy-induced harm in users of low dose ecstasy. In such circumstance, Bonferroni corrections would seriously increase the chance of Type II errors (missing a positive result), and obscure possibly important findings. In the field of ecstasy-research, missing such important findings would have
unacceptable implications for drug-policy and users of ecstasy. Nonetheless, additional research is needed to replicate the uncorrected findings.

A final limitation is that this thesis does not answer the question whether the observed sustained effects will remain after quitting the use of ecstasy for a longer period. It should be noted, however, that in none of the studies in this thesis, an association was found between neuropsychological performance and the duration of abstention from ecstasy use. The study in middle-aged ecstasy users provided more information about long term effects of ecstasy, indicating that verbal memory decrements related to ecstasy use may not be fully reversible.

**Implications and future research**

Converging evidence for a sustained negative effect of ecstasy on verbal memory was found, and therefore recreational use of ecstasy should be discouraged. It is important to distinguish between recreational ecstasy use and controlled therapeutic use of MDMA. In recreational drug use the balance between risks and benefits is different because there is no medical necessity to take the drug. In controlled therapeutic use, a balanced risk-benefit analysis should be made, as this is always important in prescribing or using medications. Potential candidates for therapeutic use should be adequately informed about all effects or side-effects of the medication that is prescribed.

Notwithstanding the plausibility of the explanations for the negative effects of ecstasy on cognition that are provided by this thesis and the compatible neuro-imaging findings provided by the two previous NeXT-dissertations \(^{51,108}\), some of the results will have to be confirmed by future studies, especially those concerning low dose ecstasy use and the genetic susceptibility to the effects of ecstasy. The findings in this thesis have answered some questions regarding the specific effects of ecstasy on neuropsychological functioning, but still some crucial questions remain unanswered.

First, it is not completely clear whether the negative effects of ecstasy on verbal memory are permanent and dose-related. A long-term follow-up of the prospective cohort is worthwhile to find out whether incidental low dose ecstasy use leaves its traces after longer periods of abstinence. Moreover, in the future, the range of the number of ecstasy tablets that is used will become larger and provide better possibilities to explore whether a dose-response relationship does exist. Also, future will tell who became regular users and who not. By then, the analyses on the predictive power of decision-making strategies can be repeated. Possibly, decision-making strategies predict frequent ecstasy use rather than first incidental ecstasy use.

Second, future research is needed to further explore interaction effects of ecstasy and concomitant drug use on neuropsychological functions. For example, the results of the study described in chapter 3 suggest that cannabis may be protective for ecstasy-related cognitive deficits. This is something to be further explored in both animal and human studies.

Third, in order to investigate whether the negative effect of ecstasy on verbal memory increases with age, leading to multiplicative memory loss, it is important to target participants beyond the age of 65. However, these individuals do not yet exist and we have to wait another 15-20 years to be able to address this research question in human beings. Meanwhile, animal studies could help to shed light on this issue.
Final conclusions

This thesis provides strong evidence for a negative sustained effect of ecstasy on verbal memory, based on several studies with both prospective and retrospective designs, both in poly-substance users and in ecstasy users with minimal exposure to other drugs, both in users of high doses of ecstasy and in users of low dose ecstasy. Moreover, there are indications for a genetic susceptibility to the effects of ecstasy. Finally, differences in punishment sensitivity might predispose to the first use of ecstasy. Future research is needed, including replication of the study in low dose novice ecstasy users, taking genetic polymorphisms into account, and more extensive investigation on the interactive effects of ecstasy and concomitant drug use, and on the effects of ecstasy in the ageing brain.